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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 41

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Filing Date: 4/16/93
Appellant(s): J.B. Weinberg and B.F. Haynes

Mary Wilson
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 7/10/96 (Paper No. 40).

(1) Status of Claims.

The statement of the status of claims contained in the Brief is correct.

This Appeal involves claims 8, 9, 11 and 14-18, as it applies to the elected species without traverse of anti-CD44 antibodies in Paper No. 28, filed 5/17/95.

(2) Status of Amendments After Final.

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

(3) Summary of Invention.

The summary of invention contained in the Brief is correct.

(4) Issues.

The appellant's statement of the issues in the Brief is incorrect.

The instant claims are rejected under 35 U.S.C. § 112, first paragraph with respect to enablement issues and not to new matter issues.

The previous rejection of claim 17 under 35 U.S.C. § 112, first paragraph, with respect to written description or new matter issues has been withdrawn (Paper No. 38) in response to applicant's amended claims, filed 4/22/96 (Paper No. 36).

(5) Grouping of Claims.

As appellant points out for each ground of rejection that applies to two or more claims, those claims do not stand or fall together for the reasons set forth in appellant's Brief.

(6) Claims Appealed.

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(7) Art of Record.

The following is a listing of the art of record relied upon in the rejection of claims under appeal.

1) Harris et al., TIBTECH 11: 42-44 (1993).
2) Edgington, Biotechnology 10: 383-393 (1992).
3) Shaffer, Biotechnology Newswatch 10/4/93, page 9.
4) Fahey et al., Clin. Exp. Immunol. 88: 1-5 (1992).
5) Hirsch et al., New Eng. J. Med. 328: 1686-1695 (1993).
6) Rivadeneira et al., Aids Research and Human Retroviruses 11: 541-546 (1995).
7) Guo et al., J. Immunol., 151: 2225-2235 (1993).
8) Paul (Ed.), Fundamental Immunology, Raven Press, NY, 1993; page 242 only.

(8) New Art.

The following page from the ATCC catalog

1) Hay et al. (Ed.), ATCC Cell Lines and Hybridomas, 8th Edition, ATCC Rockville, MD, 1994; page 416 only.

9) Grounds of Rejection.

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. § 112, First Paragraph

A) Claims 8, 9, 11 and 14-18

Claims 8, 9, 11 and 14-18, as it applies to the elected species anti-CD44 antibodies, stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

Appellant has not disclosed how to use CD44-specific antibodies therapeutically in humans. There is insufficient information or nexus of the invention with respect to the in vitro or in vivo operability of claimed therapeutic strategy to inhibit CD44-facilitated entry of HIV into cells.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs such as antibodies can be species- and model-dependent, it is not clear that reliance on the in vitro inhibition of monocyte infection by a particular HIV strain accurately reflects the relative of the claimed therapeutic strategy.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

It has been well known in the art that retroviral infections in general, and HIV infections, in particular, are refractory to anti-viral therapies. Further, it has been well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Further, as taught by Fahey et al. (Clin. Exp. Immunol., 1992), clinical trials monoclonal antibodies therapies have not provided any clinical benefits and "it is not clear how adding these additional antibodies would make a difference (see page 3, column 2, paragraph 3). Similarly, Hirsch et al. (N. Eng. J. Med., 1993) clearly teach that the success of translating promising avenues of investigation into clinical practice has been meager (page 1806, column 1, paragraph 2). For example, while soluble CD4 is a potent inhibitor of finding of certain strains of HIV-1 to CD4 cells in vitro, clinical HIV-1 isolates are less susceptible to such inhibition (page 1691, column 1, paragraph 2). Therefore, the art does

recognize the benefit of even HIV-specific or CD4-specific (versus claimed CD44-specific) inhibitors can block HIV infection clinically.

Furthermore, it is noted that Rivaderneira et al. teach CD44-specific antibodies could inhibit the monocytotropic HIV-1-BaL infectivity of monocytic cells to some degree under certain culture conditions but could not block lymphocytotropic HIV-1 infection (manuscript filed with the 12/23/93 amendment, Paper No. 18; Rivadeneira et al., Aids Research and Human Retroviruses, 1995)

Guo et al. also teach anti-CD44 antibodies did not inhibit infection (J. Immunol., 1993; see entire document, particularly page 2234, column 2, paragraph 1).

The claimed method utilizing CD44-specific antibodies appears limited to monocytic cells (versus lymphocytes) and does not completely inhibit infection of one HIV isolate in these cells under defined culture conditions. Therefore, it is not clear how the CD44-specific antibodies could inhibit HIV infection by various HIV strains in mixed leukocyte populations either in vitro or in vivo.

Concerning antibody therapy, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3)(Tibtech, 1993). Humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences.

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4). The inherent difficulties of this approach include development of serum sickness after injection of foreign protein, diminishing therapeutic effects after prolonged therapy and the potential for promotion of infection. In a brief review of adhesion therapy, Shaffer relays such concerns about monoclonal antibodies, which are promising but involve toxicities and do not seem to have a lasting effect upon repeated use (Biotechnology Newswatch, 1993).

In the absence of objective evidence or preponderance of evidence commensurate in scope with the assertions and claims, applicant has not provided predictive evidence that the claimed invention is effective as a therapeutic or preventative for HIV infection based on the in vitro inhibition of HIV infection by a particular HIV strain of monocytes in vitro alone.

B) Claim 11

Claim 11 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

It is unclear if a cell line which produces an antibody having the exact structural and chemical identity of A1G3 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species A1G3. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

In addition, the identifying information set forth in 37 CFR 1.809 (d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 11 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite in the recitation of "A1G3" because their characteristics are not known. The use of "A1G3" monoclonal antibodies as the sole means of identifying the claimed antibodies renders the claim indefinite because these terms are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct cell lines or hybridomas.

(10) Response to Argument

Rejection Under 35 U.S.C. § 112, First Paragraph

A) Claims 8, 9, 11 and 14-18

Appellant's arguments have been fully considered and are not found convincing essentially for the reasons of record.

Appellant continues to argue that the rejections of record relate more properly to a rejection under 35 U.S.C. § 101 rather than 35 U.S.C. § 112, first paragraph. Appellant continues to argue that the instant specification teaches how to make and use the invention by teaching CD44-specific antibodies, important mononuclear phagocytic target cells, the importance of said cells in HIV transmission, pharmaceutical formulations and methods of administration.

Appellant continues to argue that Rivadeneira et al. makes clear the inhibition of HIV infection of mononuclear phagocytes and asserts that the examiner appears to fault the document for not showing 100% effectiveness using CD44-specific antibodies. Again, it is not an issue of whether the instant CD44-specific antibodies are 100% effective or not.

Again, appellant is reminded that factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

In addition, appellant's arguments relying on disclosing the treatment steps as showing how to use ignores the relationship of the treatment steps to the claimed use and does not consider the invention as a whole.

Both the examiner and the appellant have agreed that the instant application has demonstrated the ability of CD44-specific antibodies to inhibit HIV infection of mononuclear phagocytes in vitro. However, the examiner and the appellant disagree whether this would be predictive of the ability of CD44-specific antibodies to inhibit HIV infection of any susceptible cell in vitro and in vivo, commensurate in scope with the claimed invention. In contrast to appellant's assertions, it is not an issue of 100% effectiveness, but rather applying the Forman factors to inhibiting HIV infection of any cell (claims 8-11) or inhibiting HIV infection in vivo (claims 8-18). It is noted that appellant asserts the skilled artisan would appreciate that in vivo and ex vivo treatments would be appropriate. Also, applicant asserts CD44-specific antibodies would be appropriate in the prevention of any susceptible host cell including blood.

It has been well known in the art that cellular CD4 has been recognized as the predominant membrane protein that interacts with HIV. However, it has been well known that HIV infection occurs in cells that express variable or no detectable levels of CD4. It has been well known that $CD4^+$ T cells are the primary target of HIV infection both in vitro and in vivo. Therefore, it would not have been predictable that targeting CD44 in mononuclear phagocytes would affect HIV infection of any susceptible cell either in vitro or in vivo. For example, either the individual or the blood would be infected by HIV via CD4, irregardless of blocking CD44 infectivity of mononuclear phagocytes. Further, it is noted that CD44-specific antibodies can block HIV infection of mononuclear phagocytes in vitro, however these same antibodies can not block the infection of mitogen-stimulated lymphocytes or cells of a T lymphocyte line in vitro (Rivadeneira et al., Aids Research and Human Retroviruses, 1995; see entire document including Abstract). Therefore applicant's assertions do not appear consistent with appellant's own observations (co-authored Rivadeneira et al., Aids Research and Human Retroviruses, 1995) that the skilled artisan can extrapolate the observations of inhibiting infection of mononuclear phagocytes by a particular HIV strain with CD44-specific antibodies under in vitro conditions to inhibiting other cell types susceptible to HIV infection even under in vitro conditions..

As indicated in the previous Office Action (Paper No. 38), claim 19 drawn to inhibiting mononuclear phagocytes in vitro is considered allowable. However, the instant claims under appeal are neither limited to in vitro inhibition or to inhibition of mononuclear phagocytes per se.

Appellant's assertions also run contrary to current understanding of the lack of predictability of HIV treatments as well as that at the time the invention was made as acknowledged in Ex parte Balzarini 21 USPQ2d 1892 (1991), which stated that skilled persons and the evidence of record supports the conclusion that in vitro testing of anti-viral compounds is not in and of itself predictive of in vivo efficacy in the treatment of retroviral diseases broadly or specifically AIDS (Balzarini, page 1896, column 2, paragraph 2).

Appellant's arguments and assertions have not been supported by sufficient information or nexus that establishes predicting the efficacy of the claimed invention for inhibiting the infection of any cell type either in vitro or in vivo commensurate in scope with the claimed methods based upon limited in vitro inhibition of mononuclear phagocytes in vitro.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective HIV-specific/adhesion-based/antibody-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting HIV infection in vivo or to all cells. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

Appellant's arguments have not been found persuasive and the rejection is maintained.

B) Claim 11

Appellant's arguments have been fully considered but are not found convincing essentially for the reasons of record.

Appellant argues that the public availability of the A1G3 antibody/hybridoma is of record, as evidence by the documentation indicating the contribution of A1G3 to the ATCC on 12//16/88 (see Paper No. 35, filed 1/18/96). Appellant continues to rely on this documentation from the ATCC that A1G3 has been publicly available since prior to April 1991. Appellant states that nothing more should be required. The examiner has maintained that this documentation is not sufficient evidence to satisfy the requirements for evidence that the deposit was made under the Budapest Treaty, the public availability and assurances that all restrictions on the accessibility will be irrevocably removed upon the granting of the patent.for the biological deposit of the A1G3 antibody/hybridoma, as required under 35 U.S.C. § 112, first paragraph. In further support of the examiner's position, the listing for the A1G3 antibody (ATCC HB-177) on page 416 of ATCC Cell Lines and Hybridomas, 8th edition, 1994 states that "this material is available under the conditions that you will not use it for commercial purposes or distribute it to third parties".

This deposit declaration regarding the submission of A1G3 antibody (ATCC HB-177) to the ATCC noted. However, this document provides no indication whether the deposit was made under conditions which are consistent with those specified in 37 CFR 1.801-1.809. Therefore, appellant has not satisfied any of the requirements for the deposit of biological materials as required under 35 U.S.C. § 112, first paragraph.

Appellant's arguments have not been found persuasive and the rejection is maintained.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Appellant's arguments have been fully considered but are not found convincing essentially for the reasons of record.

Appellant argues that A1G3 antibody has a specific meaning as evidence by the ATCC documentation referred to above (ATCC submission of A1G3; Paper No. 35, filed 1/18/96). In addition, the specification defines A1G3 as an anti-CD44 antibody given the ATCC No. HB177. Appellant argues that ATCC catalog provides the source and characteristics of the cell lines; therefore the A1G3 is not merely a laboratory designation and has clear meaning to those skilled in the art who have access via the ATCC.

It is noted that the page 416 of the 8th Edition of the ATCC Catalog states that the A1G3 antibody (ATCC HB 177) was made against the HUT 78 Sezary cutaneous T cell line and reacts with a 80 kDa protein on human medullary thymocytes. It does not recite the CD44 specificity that appellant now relies upon. Similarly, appellant's ATCC submission of A1G3 (Paper No. 35, filed 1/18/96) states the same properties and does not state the CD44 specificity.

Again, the use of the anti-CD44 "A1G3" monoclonal antibody as the sole means of identifying the claimed antibody renders the claim indefinite because this term is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct cell lines or hybridomas.

In addition as indicated above, appellant has not satisfied the deposit of the A1G3 antibody/hybridoma under 35 U.S.C. § 112, first paragraph. Since there is no evidence of a deposit or public availability, the laboratory designation would not necessarily reflect a CD44-specific antibody with the exact characteristics of the particular antibody species A1G3 antibody as required by the claimed invention.

Appellant's arguments have not been found persuasive and the rejection is maintained with respect to the recitation of A1G3 in claim 11.

(11) For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

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